Rotigotine Transdermal System

Type of Posting	Notice of Intent to Revise
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Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Rotigotine Transdermal System monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Rotigotine Transdermal System monograph to add *Drug Release Test 2*. *Labeling* information has been incorporated to support the inclusion of *Drug Release Test 2*. In this revision, a note is added to allow flexibility to use a suitable extraction solvent and extraction procedure described in the *Sample stock solution* in the *Assay* and test for *Organic Impurities*. The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

- *Drug Release Test 2* was validated using the Sunfire C18 brand of column with L1 packing. The typical retention time for rotigotine is about 2 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact V. Durga Prasad, Senior Scientist II (+91-40-4448-8723 or durgaprasad.v@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

Rotigotine Transdermal System

DEFINITION

Rotigotine Transdermal System contains NLT 90.0% and NMT 110.0% of the labeled amount of rotigotine ($C_{19}H_{25}NOS$).

IDENTIFICATION

● **A.** The UV spectrum of the rotigotine peak of the *Sample solution* corresponds to that of the *Standard solution,* as obtained in the *Assay*.

● **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

● **Procedure**

▲[Note—The *Extraction solvent* and the preparation of the *Sample stock solution* listed below are found suitable for transdermal systems that meet the requirements of *Drug Release Test 1*. Formulations labeled as meeting USP *Drug Release* test other than *Test 1* may need a different *Extraction solvent* and/or different extraction procedures to achieve complete drug extraction from the transdermal systems.]▲ (TBD)

Extraction solvent: Prepare a mixture of 2-propanol and *tert*-butylmethylether (80:20). Add 1 mL of methanesulfonic acid to 1 L of the solvent mixture.

Solution A: 0.5 mL of methanesulfonic acid in 1 L of water

Solution B: 0.5 mL of methanesulfonic acid in 1 L of acetonitrile

Mobile phase: *Solution A* and *Solution B* (65:35)

Diluent: 1 mL of methanesulfonic acid in 1 L of water

Standard stock solution: 0.5 mg/mL of USP Rotigotine Hydrochloride RS in *Extraction solvent*. [Note—Sonication in a cooled ultrasonic bath may be used to aid in dissolution.]

Standard solution: Mix 3 mL of the *Standard stock solution* with 7 mL of *Diluent*.

Sample stock solution: Nominally 0.45 mg/mL of rotigotine from NLT 10 Transdermal Systems prepared as follows. Transfer the required number of Transdermal Systems without the release liner to a suitable flask containing *N* mL of *Extraction solvent*, where *N* is the total area of the Transdermal Systems taken. Close the flask and sonicate the solution for NLT 10 min in a sonicator maintained at 20°, shaking the flask intermittently to ensure the silicone matrix is completely dissolved. [Note—Sonication time may be extended if needed to enable complete dissolution of the silicone matrix.]

Sample solution: Mix 3 mL of *Sample stock solution* with 7 mL of *Diluent*. Centrifuge the solution and use the clear supernatant. [Note—A centrifuge speed of NLT 4000 rpm for NLT 15 min may be used.]

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 272 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.0-mm × 7.5-cm; 4-µm packing L7

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 10 µL

Run time: NLT 4 times the retention time of rotigotine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.2

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rotigotine ($C_{19}H_{25}NOS$) in each Transdermal System taken:

$$\text{Result} = (r_U/r_S) \times C_S \times (V/N) \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Rotigotine Hydrochloride RS in the *Standard stock solution* (mg/mL)

V = volume of the *Sample stock solution* (mL)

N = number of Transdermal System units used to prepare the *Sample stock solution*

M_{r1} = molecular weight of rotigotine, 315.47

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

L = label claim (nominal content) of rotigotine in each Transdermal System (mg/unit)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DRUG RELEASE** ⟨724⟩

▲Test 1▲ (TBD)

Medium: Dissolve 6.9 g of monobasic sodium phosphate in 1 L of water. Adjust with a suitable concentration of sodium hydroxide or phosphoric acid to a pH of 4.5; 900 mL, deaerated.

Apparatus 5: 50 rpm; Transdermal System on metal disk

Times: 15, 30, 60, and 180 min

Solution A, Solution B, and **Mobile phase:** Prepare as directed in the *Assay*.

Standard solution: (L/800) mg/mL of USP Rotigotine Hydrochloride RS in *Medium*, where L is the label claim in mg/unit

Sample solution: Withdraw 2 mL from the vessel at the specified times.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 272 nm

Column: 4.0-mm × 7.5-cm; 4-µm packing L7

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 50 µL

Run time: NLT 2.5 times the retention time of rotigotine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.2 for rotigotine

Relative standard deviation: NMT 2.0% for rotigotine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount (nominal content) of rotigotine ($C_{19}H_{25}NOS$) released at each time point *i*:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Rotigotine Hydrochloride RS in the *Standard solution* (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (nominal content) of rotigotine in the Transdermal System (mg/unit)

M_{r1} = molecular weight of rotigotine, 315.47

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

Acceptance criteria: See *Table 1*.

Table 1

Time Point (*i*)	Time (min)	Rotigotine Released (%)
1	15	14–34
2	30	27–47
3	60	45–65
4	180	NLT 85

The percentages of the labeled amount of rotigotine ($C_{19}H_{25}NOS$) released at the times specified conform to *Drug Release* ⟨724⟩*, Acceptance Table 1*.

▲**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Drug Release Test 2*.

Medium: 10 mM phosphate buffer, pH 4.5 (Dissolve 1.36 g of potassium phosphate, monobasic in 1 L of water. Adjust with a suitable concentration of potassium hydroxide or phosphoric acid to a pH of 4.5.); 900 mL

Apparatus 5: 50 rpm

Times: 5, 15, 240, and 720 min

Buffer: Dissolve 6.8 g of potassium phosphate, monobasic in 1 L of water. Adjust with a suitable concentration of potassium hydroxide or phosphoric acid to a pH of 4.5.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Standard solution: (*L*/900) mg/mL of rotigotine prepared from USP Rotigotine Hydrochloride RS in *Medium*, where *L* is the label claim in mg/unit. Sonicate, if necessasary.

Sample solution: Use the portion of the solution withdrawn from the vessel at the specified times.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 224 nm

Column: 3.0-mm × 10-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 2 times the retention time of rotigotine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rotigotine ($C_{19}H_{25}NOS$) released at each time point (*i*):

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of rotigotine from the *Sample solution*

r_S = peak response of rotigotine from the *Standard solution*

C_S = concentration of USP Rotigotine Hydrochloride RS in the *Standard solution* (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim of rotigotine in the Transdermal System (mg/unit)

M_{r1} = molecular weight of rotigotine, 315.48

M_{r2} = molecular weight of rotigotine hydrochloride, 351.93

Acceptance criteria: See *Table 2*.

Table 2

Time Point (*i*)	Time (min)	Amount Released (%)
1	5	20–45
2	15	40–65
3	240	60–85

Time Point (*i*)	Time (min)	Amount Released (%)
4	720	NLT 80

The percentages of the labeled amount of rotigotine ($C_{19}H_{25}NOS$) released at the times specified conform to *Drug Release* ⟨724⟩, *Acceptance Table 1*. ▲ (TBD)

- **Uniformity of Dosage Units** ⟨905⟩**:** Meets the requirements

IMPURITIES

Change to read:

- **Organic Impurities**

▲[Note—The *Extraction solvent* and the preparation of the *Sample stock solution* listed below are found suitable for transdermal systems that meet the requirements of *Drug Release Test 1*. Formulations labeled as meeting USP *Drug Release* test other than *Test 1* may need a different *Extraction solvent* and/or different extraction procedures to achieve complete drug extraction from the transdermal systems.] ▲ (TBD)

Extraction solvent, Solution A, Solution B, Diluent, and **Standard stock solution:** Prepare as directed in the *Assay*.

Mobile phase: See ▲*Table 3*.

Table 3 ▲ (TBD)

Time (min)	Solution A (%)	Solution B (%)
0	95	5
2.0	95	5
35	40	60
38	40	60
39	95	5

Impurities stock solution: 0.1 mg/mL each of USP Rotigotine Related Compound C RS and USP Rotigotine Related Compound K RS in 2-propanol

System suitability stock solution: 0.15 mg/mL of USP Rotigotine Hydrochloride RS and 0.0025 mg/mL each of USP Rotigotine Related Compound C RS and USP Rotigotine Related Compound K RS from suitable volumes of *Standard stock solution* and *Impurities stock solution* in *Extraction solvent*

System suitability solution: Mix 3 mL of *System suitability stock solution* with 7 mL of *Diluent*.

Sensitivity stock solution: 0.25 µg/mL of USP Rotigotine Hydrochloride RS from *Standard stock solution* in *Extraction solvent*

Sensitivity solution: Mix 3 mL of *Sensitivity stock solution* with 7 mL of *Diluent*.

Sample stock solution: [Note—Lacquer removal is recommended to minimize the interferences from the lacquer with the degradation product peaks as follows. Remove the lacquer from the backing foil of

each Transdermal System with 4% (v/v) glacial acetic acid in methanol. Dry the lacquer-removed Transdermal Systems for NLT 1 h at room temperature.] Nominally 0.45 mg/mL of rotigotine from NLT 3 Transdermal Systems prepared as follows. Transfer the required number of (lacquer removed, if necessary) Transdermal Systems without the release liner to a suitable flask containing *n* mL of *Extraction solvent*, where *n* is the total area (cm^2) of the Transdermal Systems taken. Close the flask and sonicate the solution for NLT 10 min in a sonicator maintained at 20°, shaking the flask intermittently to ensure the silicone matrix is completely dissolved. [NOTE—Sonication time may be extended if needed to enable complete dissolution of the silicone matrix.]

Sample solution: Mix 3 mL of *Sample stock solution* with 7 mL of *Diluent*. Centrifuge the solution and use the clear supernatant. [NOTE—A centrifuge speed of NLT 4000 rpm for NLT 15 min may be used.]

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L10. [NOTE—A guard column with dimensions 4-mm × 1-cm with 5-µm L3 packing is recommended to minimize interference from the adhesive.]

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 80 µL

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[NOTE—See ▲*Table 4*▲ (TBD) for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between rotigotine related compound K and rotigotine related compound C, *System suitability solution*

Signal-to-noise ratio: NLT 10 for rotigotine, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each specified or unspecified degradation product in the portion of the Transdermal System taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each specified or unspecified degradation product from the *Sample solution*

r_T = sum of all the peak responses (including the rotigotine peak) from the *Sample solution*

F = relative response factor (see ▲*Table 4*▲ (TBD))

Acceptance criteria: See ▲*Table 4*.

Table 4▲ (TBD)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desthienylethyl rotigotine[a]	0.36	1.0	0.40
Rotigotine related compound K	0.6	3.5	0.20
Rotigotine related compound C	0.7	1.0	0.60
Rotigotine	1.0	—	—
Any individual unspecified degradation product	—	1.0	0.20
Total degradation products	—	—	1.0

[a] (*S*)-6-(Propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Change to read:

- **LABELING:** The label states the total amount of rotigotine in the Transdermal System and the release rate, in mg/day, for the duration of the application of one system.

▲When more than one *Drug Release* test is given, the labeling states the *Drug Release* test used only if *Test 1* is not used.▲ (TBD)

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Rotigotine Hydrochloride RS

(6*S*)-6-[Propyl(2-(2-thienyl)ethyl)amino]-5,6,7,8-tetrahydro-1-naphthalenol hydrochloride.

$C_{19}H_{25}NOS \cdot HCl$ 351.93

USP Rotigotine Related Compound C RS

(*S*)-6-{[2-(Thiophen-2-yl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-1-ol.

$C_{16}H_{19}NOS$ 273.39

USP Rotigotine Related Compound K RS

7,8-Dihydronaphthalen-1-ol.

$C_{10}H_{10}O$ 146.19

Page Information:

Not Applicable

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